AT

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/819,266	03/28/2001	Agamemnon Antoniou Epenetos	JG-EPC-4955P/500563.20004	4300

26418 7590 05/04/2004

REED SMITH, LLP
ATTN: PATENT RECORDS DEPARTMENT
599 LEXINGTON AVENUE, 29TH FLOOR
NEW YORK, NY 10022-7650

EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 05/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/819,266	EPENETOS, AGAMEMNON ANTONIOU	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,10-16,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 10-16, 21-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☑ Interview Summary (PTO-413) Paper No(s)/Mail Date. 19/04/04
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 1, 3, 10-16, 21-22 are being examined.

The following are the remaining rejections.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Rejection under 35 USC 112, first paragraph of claims 1, 3, 10-16, 21-22 pertaining to lack of a clear written description of "a portion for binding to a specific target cell" remains for reasons already of record in paper No.17.

Applicant argues that besides antibodies, non-antigenic molecules such as receptors for melanocyte-stimulating hormones (MSH) and vascular endothelial growth factors (VEGH) are recited.

Applicant recites *In re Herschler*, stating that according to *Herschler* and the final Written Description Guidelines, the present claims satisfy the written description requrirement, because one of skill in the art would be led to the class of compounds that satisfy the limitation "a portion for binding to a specific target cell" by the functional recitation of that class of compounds.

Applicant further asserts that as in *Amgen v. Hoechst Marion Roussel, Lilly* does not control the present situation, because "a portion for binding to a specific target cell" is not new or unknown biological material.

The recitation of the case laws *In re Herschler* and *Amgen v. Hoechst Marion Roussel* is acknowledged.

Applicant's arguments set forth in paper of 01/26/04 have been considered but are not deemed to be persuasive for the following reasons:

Contrary to Applicant's arguments, "a portion for binding to a specific target cell" encompasses numerous compounds with unknown structure, and thus the teaching of *Amgen v. Hoechst Marion Roussel* does not apply to the instant application.

The following is the teaching of the court in *Randolph J. Noelle v Seth Lederman, Leonard Chess and Michael J. Yellin* (CAFC, 02-1187, 1/20/2004), which clearly applies to the instant invention:

"Since the Board's decision in Staehelin, this court has subsequently held that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See Enzo Biochem II, 323 F.3d at 965; Regents, 119 F.3d at 1568."

In the present application, since only a limited number of specific species, antibodies and receptors for MSH and VEGH are recited as known structure for "a portion for binding to a specific target cell", Applicant cannot claim a genus.

Further, the following teaching of the court in *ROCHESTER v. G.D. SEARLE & CO., INC.*, February 13, 2004, also applies to the present application:

While it is true that this court and its predecessor have repeatedly held that claimed subject matter "need not be described in haec verba" in the specification to

satisfy the written description requirement, e.g., In re Smith, 481 F.2d 910, 914 (CCPA 1973), it is also true that the requirement must still be met in some way so as to "describe the claimed invention so that one skilled in the art can recognize what is claimed." Enzo, 323 F.3d at 968.

> [T]he appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. . . . A description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) described even in terms of its function of lessening inflammation of tissues fails to distinguish any steroid from others having the same activity or function. A description of what a material does, rather than of what it is, usually does not suffice. [Regents of the Univ. of Cal. v.] Eli Lilly [& Co., Inc.], 119 F.3d [1559,] 1568 [(Fed. Cir. 1997) ("Lilly")] . . . . The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. Id.

Similarly the court in *Lilly* also stated that:

> a generic statement such as vertebrate insulin cDNA or mammalian insulin cDNA without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus,

> visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

In the instant application, a definition by function, and "naming a type of material generally known to exist", without knowledge of what the genus of "a portion for binding to a specific target cell" consists of, is not a description of the claimed material.

Further, the following is the teaching of Enzo, which also clearly applies to the claimed invention:

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

In the instant application, the specification does not disclose "sufficiently detailed, relevant identifying characteristics, functional characteristics of "a portion for binding to a specific target cell", that is coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics", and thus does not meet the requirement by Enzo. The specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

In view of the above, and in previous Office action, one would conclude that Applicant did not have in possession of "a portion for binding to a specific target cell" conjugated to a cytotoxic portion at the time of filing.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. Rejection under 35 USC 112, first paragraph of claims 1, 3, 10-16, 21-22 pertaining to lack of enablement for "a portion for binding to a specific target cell" conjugated to a cytotoxic portion, remains for reasons already of record in paper No.17.

Applicant asserts that numerous examples of antigenic targeting molecules, such as antibodies, and non-antigenic targeting molecules, such as receptors are disclosed generically and with specific examples.

Applicant's arguments set forth in paper of 01/26/04 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that "a portion for binding to a specific target cell" encompasses numerous ligands with unknown structure, such as small molecules or mimetics of the binding target on the cell.

Applicant has not taught the structure of "a portion for binding to a specific target cell", other than antibodies and receptors for MSH and VEGH. Applicant has not taught how to make such a portion such that it could function as claimed.

2. Rejection under 35 USC 112, first paragraph of claims 1, 3, 10-16, 21-22 pertaining to lack of enablement for "any constitutively active caspase" conjugated to a portion for binding to a specific target cell, remains for reasons already of record in paper No.17.

Applicant argues that "constitutively active caspase" describes a caspase that is active without interacting with any other factors or molecules. Applicant further argues that the mere autocatalysis and constitutively active is defined clearly in the art, e.g. Srinivasula et al.

Applicant further argues that at Example H the claimed conjugate possessing a constituvely active caspase is effective in producing an apoptotic effect in the presence of serum in the culture medium. Applicant asserts that therefore, the Examiner's hypothesis that activated caspases would be inhibited by protease inhibitors present in the serum before reaching the target cell may be rejected.

Applicant's arguments set forth in paper of 01/26/04 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that the specification discloses that by "a constitutively active caspase", we "include" a protein or peptide which exhibits cysteine-bearing aspartate protease activity sufficient to induce apoptosis, i.e. "a caspase in an activated form", or alternatively the constitutively active caspase "may" comprise a precursor of such an active caspase that is able to spontaneously self-catalyse its conversion to the active caspase (p.10, second paragraph).

The definition of "a constitutively active caspase" in the specification is not limiting. Clearly "a constitutively active caspase", as defined in the specification, encompasses any protein, and thus one would not know to make the claimed conjugate such that it functions as claimed.

In addition, the definition of "a constitutively active caspase" by Srinivasula is not germane, given the non-limiting definition of "a constitutively active caspase" in the instant specification.

Further, "a constitutively active caspase" could also include caspases in activated forms, and not just limited to a conjugate of caspase-3 or 6, wherein the subunit positions are reversed such that the C-terminus of the large subunit and the N-terminus of the small subunit are free, while the N-terminus of the large subunit and the C-terminus of the small subunit are physically linked, and wherein said re-arranged caspase could spontaneously fold and allows an active site to be formed, without the requirement of a protease cleavage, as disclosed in the specification (specification, page 11, paragraph before last).

Based on the teaching of Grabarek et al, Stief et al, Djie et al, Bjartell et al, and Schimmer et al, all of record, one would expect that serine protease inhibitors or caspase inhibitors in the serum could readily bind to, form a stable complex, and inactivate activated caspases, via their exposed active serine protease site, before the caspases could reach the proper sites for action.

Moreover, "a constitutively active caspase" could also include wild type caspases, such as pro-caspase-3, which are poor inducer of cell death, because of their inability to autoactivate, as taught by Colussi et al, of record). Thus based on the teaching of Colussi et al, and in the specification, one cannot predict that the claimed conjugate would be useful for anything, in view of their being ineffective in inducing apopotis.

Further, concerning Example H, the assay medium contains CEA-expressing cells in 10% serum, and thus it is questionable whether said assay medium would contain a representative concentration of protease inhibitors in the blood. It is well known in the art that the degree of inhibition of activity of caspases depends on the concentration of the inhibitors. For example, Srinivasula et al teach that inhibition of the autocatalytic re-arranged caspase-3 or 6 depends on the concentration of the inhibitors, wherein nearly 50-90% inhibition of the re-arranged caspase-3 occurs at a concentration of 40-400 nM of the inhibitor DEVD-CHO (p.10109, first column, last paragraph).

3. Rejection under 35 USC 112, first paragraph of claims 21-22 pertaining to lack of enablement for a pharmaceutical composition comprising a constitutively active

caspase" conjugated to a portion for binding to a specific target cell, or a compound for use in medicine, remains for reasons already of record in paper No.17.

Applicant argues that at Example H, the claimed conjugate possessing a constituvely active caspase is effective in producing an apoptotic effect in the presence of serum in the culture medium, supra, and thus is relevant for in vivo application.

This argument is not persuasive, because the culture medium contains only 10% serum and would not representative of in vivo conditions, supra. Further, Srinivasa et al teach that the autocatalytic re-arranged caspase-3 or 6 could be inhibited by caspase inhibitors, wherein nearly 50-90% inhibition of the re-arranged caspase-3 occurs at a concentration of 40-400 nM of the inhibitor DEVD-CHO (p.10109, first column, last paragraph). In addition, based on the teaching of Grabarek et al, Stief et al, Djie et al, Bjartell et al, and Schimmer et al, all of record, one would expect that serine protease inhibitors or caspase inhibitors in the serum in vivo could readily bind to, form a stable complex, and inactivate the claimed re-arranged caspases, via their exposed active serine protease site, before the caspases could reach the proper sites for action.

Applicant further argues that although Schimmer teaches that inhibitory molecules may be over-expressed in cancer cells, it is also well known that many genes are underexpressed in some cancer cells, e.g. DNA repair enzymes. Applicant asserts that therefore, a skilled artisan would also reasonably predict that such inhibitory molecules might also be under-expressed, exacerbating the effectiveness of the conjugates of the invention.

This argument is not persuasive, because there is no reference confirming Applicant's assertion that a skilled artisan would also reasonably predict that such inhibitory molecules might also be under-expressed, exacerbating the effectiveness of the conjugates of the invention. On the contrary, Schimmer et al clearly teach that cancer cells could overexpress endogenous inhibitors of the effector caspases and block the caspase pathways.

In addition, contrary to Applicant's assertion that the administration of chemotherapeutics and treatment of cancer is a well-established and predictable art, the art overwhelmingly teaches that cancer therapy is highly unpredictable, as taught by Gura et al, Jain et al, Curti et al, and Hartwell et al, all of record.

Thus it is unpredictable that the claimed caspase would be useful for in vivo use as a therapeutic agent in medicine.

REJECTION UNDER 35 USC 103

Claims 1, 3, 10-16, 21-22 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Srinivasula et al, in view of US 4,753,894, Colussi, PA et al, and Keppler-Hafkemeyer A et al, for reasons already of record in paper No.17.

Applicant argues that there is no motivation to combine the references.

Applicant argues that Srinivasula et al only teach the rearrangement of domains of caspase 3 in order to create an autoactivating caspase, and that the rearranged caspases should be used in gene therapy.

Applicant argues that a skilled person would understand the teaching of Colussi et al. to show that a variety of factors could come into play in terms of the inhibition of caspases, and that inhibition is not even guaranteed to occur. Applicant argues htat furthermore, the skilled person would also relate the teachings on inhibition to the other key teachings of Colussi et al, namely, that to create an auto-activating molecule that is not inhibited, a fusion of procaspase 3 and a caspase 2 domain is preferred. Applicant argues that would be only reasonable for the skilled artisan to assume that the creation of a procaspase 3-caspase 2 fusion would be the instrumental factor in producing a caspase that is not inhibited.

Applicant asserts that in any event, a combination of these two references would still follow a gene therapy approach, in complete contrast to the present invention.

Applicant further asserts that it is shown that apoptosis plays only a minor role in induction of cell death by Ricin A-mediated cell death when compared to the extent of the role of protein synthesis inhibition. Applicant concludes that therefore, it would not be obvious to replace the molecule with an important and major mechanism of cell death being inhibition of protein synthesis, with a molecule that expresses only a minor mechanism of cell death, namely, apoptosis.

Applicant's arguments set forth in paper of 01/26/04 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that the claims are drawn to a protein composition and not to a method. Therefore, the intention of Srinivasula et al for use of the rearranged caspases, which are exactly the same as the rearranged caspases of the claimed conjugate, for

gene therapy is not germane here, because of the following reasons: 1) a composition could be used for several purposes, 2) proteins are encoded by polynucleotides, and 3) the rearranged caspase proteins are taught by . Srinivasula et al.

Further, the reference by Colussi et al is recited to show that the autoactivated caspase taught by Colussi et al is the same as the broadly claimed caspase of the claimed conjugate.

Further the motivation for combining the references clearly flows from the teaching in the art. That is: 1) using antibody as a carrier for targeting compounds to specific cells is well known in the art, 2) making an immunotoxin by combining a ligand such as an antibody specific to a target cell to ricin A, Pseudomona exotoxin A (PE), a cytotoxic comound, which could kill cell via apoptosis pathway is well known in the art, as taught by US 4,753,894, and Keppler-Hafkemeyer A et al, and 2) Therefore, it would have been obvious to make an immunotoxin by replacing the apoptosis inducing compound in the composition taught by US 4,753,894, and Keppler-Hafkemeyer A et al with the rearranged caspases taught by Srinivasula et al or the autoactivated caspases-2 and 3 conjugate taught by Colussi et al, which caspases could be readily used at very low concentration to induce apoptosis in target tissues or tumor, as taught by Srinivasula et al and Colussi et al.

In addition, it would have been obvious to replace ricin A or PE which could kill cell via either protein synthesis or via apoptosis with the rearranged caspases taught by Srinivasula et al or the autoactivated caspases-2 and 3 conjugate taught by Colussi et al, because the conjugates taught by the combined art are more specific caspase

inhibitors than ricin A or PE conjugates, and increase the numbers of immunotoxins available for therapy, widening the treatment window of different types of cancers, having different susceptibility to apoptotic mechanisms (Keppler-Hafkemeyer A et al, page 16941, second column, last paragraph, bridging page 16942).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, YVONNE EYLER can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

April 16, 2004